REMARKS

Claims 1-13 are pending in the application. Claims 1, 2, and 6-10 have been amended. New claims 11-13 have been added. Support for the amendments and new claims can be found in the specification at, e.g., page 2, paragraph 0007, and page 16, paragraph 0064. No new matter has been added.

Allowable Subject Matter

At page 8 of the Office Action, the Examiner stated that claims 3-5 are allowed. In view of the remarks presented herein, applicants respectfully submit that all of the pending claims are now in condition for allowance.

35 U.S.C. §112, First Paragraph (Written Description)

At pages 2-5 of the Office Action, claims 1, 2, and 6-10 were rejected as allegedly containing subject matter that was not described in the specification in such a way that one skilled in the art can reasonably conclude that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse the rejection in view of the following remarks.

The present application describes the identification and characterization of the human RetL3 protein (SEQ ID NO:21) and the murine RetL3 protein (SEQ ID NO:17). These two species of RetL3 are 76.8% identical to each other (see specification at page 37, paragraph 0116). Given that each of the disclosed RetL3 proteins constitutes a functional polypeptide that interacts with the receptor tyrosine kinase Ret, the skilled person would readily expect that at least those amino acids that diverge between the two RetL3 species (i.e., 23.2% of the amino acid positions) are likely to be amenable to change without eliminating biological activity.

Consistent with the specification's disclosure of species of RetL3 that are 76.8% identical to each other, independent claim 1 is directed to an isolated polypeptide that (i) comprises an amino acid sequence that is at least 80% identical to the sequence of SEQ ID NO:17 or SEQ ID

NO:21, and (ii) interacts with and triggers dimerization or autophosphorylation of the receptor protein Ret. The genus of polypeptides encompassed by claim 1 does not have substantial variation, since all such polypeptides must have a specified activity and contain a sequence that is at least 80% identical to SEQ ID NO:17 or SEQ ID NO:21. The human and murine RetL3 polypeptides disclosed in the specification are representative of the claimed genus because: all members of the genus are highly similar to a reference sequence (SEQ ID NO:17 or SEQ ID NO:21); and routine assays are well known in the art for identifying variants having the functional activity specified by the claim. In light of the disclosure contained in the application as filed, the skilled artisan would have concluded that the inventors were in possession (at the time of filing of the present application) of the necessary common attributes possessed by the members of the claimed genus.

The Office Action cited *Regents of the University of California v. Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), a leading case on the written description requirement for nucleic acid molecules, in support of the present rejection. The discussion in *Lilly* regarding a proper written description for genus claims had to do with a claim drawn to a vertebrate mRNA encoding insulin. The *Lilly* court held that a generic statement, such as the term "mammalian insulin cDNA" is not, without more, an adequate written description of an invention claiming the nucleotide sequence for human insulin. The court's decision in *Lilly* focused on functional claims directed merely to a desired result without structure: "[t]he description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention." *Id.* at 1406. However, the *Lilly* court also took care to indicate that structural information about the claimed genus was different in kind than a mere desired result. The court indicated that in claims involving chemical materials such as proteins and polynucleotides "generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is usually an adequate description of the claimed genus." *Id.*

Claim 1 is drawn to a polypeptide structurally defined by the degree of identity to a reference sequence. The claim thus provides a precise definition of the invention by structure, as is generally required for an adequate description of a protein sequence. Moreover, the claimed invention is also defined by the recited function of the polypeptide (i.e., the ability to interact with and trigger dimerization or autophosphorylation of the receptor protein Ret). The claim is not directed to a mere desired result without structure, as was the case in *Lilly*. A person of ordinary skill in the art would clearly understand the structural definition of the polypeptide provided by claim 1 and would therefore understand the inventors to have been in possession of the claimed polypeptide at the time the application was filed. Accordingly, independent claim 1 and claims 2 and 6-10 that depend therefrom satisfy the written description requirement. Applicants request that the Examiner withdraw the rejection.

35 U.S.C. §112, First Paragraph (Enablement)

At pages 5-7 of the Office Action, claims 1, 2, and 6-10 were rejected as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse the rejection in view of the following remarks.

As detailed above, independent claim 1 is directed to an isolated polypeptide that (i) comprises an amino acid sequence that is at least 80% identical to the sequence of SEQ ID NO:17 or SEQ ID NO:21, and (ii) interacts with and triggers dimerization or autophosphorylation of the receptor protein Ret. For the following reasons, a person of ordinary skill in the biological arts at the time of filing of the present application would have been able to make and use the claimed polypeptide without undue experimentation and with a reasonable expectation of success.

It is well within the grasp of the biologist of ordinary skill to prepare a polypeptide that is at least 80% (or at least 90% or 95%) identical to the RetL3 sequence of SEQ ID NO:17 or SEQ ID NO:21. For example, standard mutagenesis techniques can be used produce variants of RetL3. Given that the human and murine RetL3 proteins (both of which are disclosed in the

specification) differ at 23.2% of their amino acid positions, the skilled person would expect that at least those amino acids that diverge between the two species are likely to be amenable to change without eliminating biological activity. In view of the specification's disclosure of human and murine RetL3, combined with the knowledge in the art that conservative amino acid substitutions can be made in a protein so as to reduce the likelihood that a given amino acid change will result in a loss of function, it would have required no undue experimentation for the skilled person to prepare a polypeptide that contains an amino acid sequence that is at least 80% identical to SEQ ID NO:17 or SEQ ID NO:21 and that is expected to retain the RetL3 biological activity recited in the claims.

In addition to having been able to produce RetL3 sequence variants having at least 80% (or at least 90% or 95%) identity with SEQ ID NO:17 or SEQ ID NO:21, it would have required no undue experimentation for the skilled artisan to identify those variants that retain the ability to interact with and trigger dimerization or autophosphorylation of the receptor protein Ret (i.e., the functional activity recited in the claims). Readily screenable assays can be used to determine whether a given protein possesses this functional activity.

The Office Action cited Lederman et al. (1991) Molecular Immunology 28:1171-81 ("Lederman") in support of the present rejection. Lederman describes the effect of a single amino acid substitution in the CD4 protein on the binding of a particular monoclonal antibody (OKT4) to the protein. The investigation by Lederman of the functional importance of a single CD4 amino acid residue for OKT4 binding fails to negate the patentability of the polypeptide of claim 1. Although it is possible in certain cases to abolish the functional activity of a protein by mutating a critical amino acid residue (as described by Lederman), this in no way suggests that a person of ordinary skill in the art cannot readily make functional variants of a given protein (e.g., RetL3) without undue experimentation. The skilled person would expect that a significant percentage of even random substitutions in a given protein will result in mutated proteins with full or nearly full activity. These are far better odds than those at issue in *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988), in which the court found that screening many hybridomas to find the few that fell within the claims was not undue experimentation. The question is not whether it

is possible to abolish activity of a given protein by introducing a point mutation, but rather whether one of ordinary skill can produce, without undue experimentation, mutants in which the activity is not abolished.

In light of the foregoing remarks, applicants respectfully submit that one of ordinary skill in the art would have been able, at the time of filing of the present application, to make and use the claimed polypeptides without undue experimentation and with a reasonable expectation of success. Accordingly, applicants request that the Examiner withdraw the rejection of independent claim 1 and dependent claims 2 and 6-10.

35 U.S.C. §112, Second Paragraph (Indefiniteness)

At page 7 of the Office Action, claims 2 and 6 were rejected as allegedly indefinite for failing to further limit claim 1.

Applicants respectfully traverse the rejection in view of the following remarks.

Independent claim 1 is directed to an isolated polypeptide comprising an amino acid sequence that is at least 80% identical to the sequence of SEQ ID NO:17 (murine RetL3) or SEQ ID NO:21 (human RetL3). Claim 2 depends from and further limits claim 1 by requiring that the "amino acid sequence" recited in claim 1 be at least 80% identical to the sequence of SEQ ID NO:17 (murine RetL3). Similarly, claim 6 depends from and further limits claim 1 by requiring that the "amino acid sequence" recited in claim 1 be at least 80% identical to the sequence of SEQ ID NO:21 (human RetL3). Because dependent claims 2 and 6 each limit (in different ways) the "amino acid sequence" recited in claim 1, the claims are in proper dependent format and satisfy the definiteness requirement. As a result, applicants request that the Examiner withdraw the rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Enclosed is a Petition for One Month Extension of Time. The extension of time fee in the amount of $120 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply other any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13751-045003.

Respectfully submitted,

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